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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,141	08/18/2003	Stephen L. Hutcherson	C01037.70049.US	3287

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Helen C. Lockhart
Wolf, Greenfield & Sacks, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
HUMPHREY, DAVID HAROLD	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,141	HUTCHERSON ET AL.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments and Amendments

1. Claims 26-48 are pending.

Claims 26, 34, 35, 37, 38, 45, 46, and 48 are amended.

Claims 26-48 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections

Claim Rejections - 35 USC § 112, first paragraph

3. The rejection of claims 26-48 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for containing new matter is maintained. The claims have been amended to recite "not antisense" as a limitation, however, the addition of the term "not antisense" do not find support in the specification as filed.

Applicants argue that the instant specification describes oligonucleotide analogs having "both therapeutic efficacy (through antisense or other means) and immunopotentiating activity" on page 8, lines 6-7. Applicants conclude that since the specification gives a number of alternatives for the activity of phosphorothioate oligonucleotide analogs, the specification provides support for the term "not antisense".

Applicants' arguments have been carefully considered but found not persuasive. The therapeutic efficacy of antisense is that it inhibits the expression of the target protein. The portion of the specification cited by Applicants refers to the effects of the oligonucleotide analogs NOT the structure. The limitation of "not antisense" is clearly a reference to the structure of the oligonucleotide and not the activity as claimed by Applicants. Similarly, the term "other means" relates to the manner in which the oligonucleotides could stimulate an immune response and not to the structure of the olignocleotides.

4. The rejection of claims 26-48 under 35 U.S.C. 112, first paragraph, as containing subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was fled, had possession of the claimed invention, is maintained.

The specification does not reasonably provide a written description for a method for stimulating an immune response in a human comprising administering an amount of a phosphorothioate oligonucleotide analog effective to stimulate an immune response. Thus, the full scope of the claims is a method that utilizes any phosphorothioate oligonucleotide analog to stimulate an immune response. This encompasses a huge number of possible phosphorothioate oligonucleotide analog sequences.

Applicants argue that the instant specification describes oligonucleotide analogs with at least one phosphorothioate bond in the backbone and these oligonucleotides can induce stimulation of a cell-mediated or humoral immune response in a sequence

non-specific manner, see Remarks, page 7, lines 3-6. Applicants further argue that since the teachings of McIntyre et al. are directed to a humoral immune response, they are not applicable to the amended claims directed to a cell-mediated immune response.

Applicants' arguments have been carefully considered but found not persuasive. The Examiners citation of McIntyre et al. was to illustrate that Applicants were not in possession of the genus of phosphorothioate oligonucleotide analogs that are not antisense and that stimulate an immune response. In order to determine whether or not Applicants have provided sufficient written description for the claimed invention, the factors that must be considered are the disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, and structure/function correlation. In this case, the only factor present is the sequence of three phosphorothioate oligonucletides analogs. Only one of these, SEQ ID NO: 1, also referred to in the specification as ISIS 2105, an antisense phosphorothioate oligonucleotide analog, is administered to patients to elicit a local immune response, see Specification, Examples 9-12. Other than the three sequences SEQ ID NOs: 1, 2, and 3 (see Specification page 12, lines 7-9), only one of which was actually administered and shown to elicit a local immune response, no other sequences are provided that would indicate that Applicants are in possession of the genus of phosphorothioate oligonucleotide analogs that elicit an immune response. It is also noted that none of the sequences satisfy the claim limitation "not antisense". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the

claimed genus and one of ordinary skill in the art would conclude that Applicant was not in possession of the broadly claimed genus.

5. The rejection of claims 26-48 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method of stimulating a local immune response in a human by administering one phosphorothioate oligonucleotide analog, ISIS 2105, does not reasonably provide enablement for a method of stimulating a humoral immune response in a human using any phosphorothioate oligonucleotide analogs in a patient with any type of cancer, any type of infection, and in combination with any type of surgery, is maintained.

Applicants' arguments have been carefully considered but found not persuasive. Applicants argue that one unexpected finding of the present invention is that oligonucleotides having at least one phosphorothioate linkage in their backbone can stimulate immune responses in a sequence independent manner, see Remarks, page 8, lines 4-6. The Examiner was unable to find support for this assertion in the specification as filed. The specification does not seem to disclose the "unexpected finding" that Applicants are now arguing which is that the phosphorothioate oligonucleotides stimulate an immune response in a sequence independent manner.

Applicants further argue the references cited by the Examiner to demonstrate the state of the art and the level of unpredictability in the art. For example, Applicants argue that Allison et al. (Molecular Immunology 28: 279-284, 1991) cited by the Examiner shows the traditional way an immune response is evaluated which is by measuring

antibody types and levels. Applicants argue that the instant specification demonstrates the efficacy of the phosphorothioate oligonucleotides in both antibody production and cytokine production in the Examples, see Remarks, page 8, third full paragraph, lines 12-16. The Examiner does not concur. The specification demonstrates an immune response by administering only *one* antisense phosphorothioate, ISIS 2105 in rats (Example 7, pages 23 and 24) and mice (Example 8, pages 24 and 25) and humans (Examples 9-11, pages 25 and 26). Thus, the data provided in the specification is not commensurate in scope with the claims, which are drawn to methods of stimulating an immune response using any phosphorothioate oligonucleotide analogs.

Applicants argue that the three references cited by the Examiner as evidence that "induction of splenomegaly and stimulation of B-lymphocyte proliferation in mice injected with phosphorothioate oligos occurs unpredictably in a manner that is dependent on the nucleotide sequence of the phosphorothioate oligonucleotide analogs" does not support the Examiners' broad conclusion that this was known or widely accepted in the art at the time the instant application was filed and that "each of these references represents a very small number of examples and the effects may be explained by antisense activity," see Remarks, page 9, lines 5-9. The Examiner does not concur. Ratajczak et al. (Proc. Natl. Acad. Sci. USA 89: 11823-11827, 1992) teach the administration of sequence specific sense, antisense, and control phosphorothioate oligonucleotides to mice result in different responses depending on the sequence administered, see page 11825, left column, third full paragraph, lines 16-27.

In response to the Vollmer et al. (Antisense and Nucleic Acid Drug Development

12: 165-175, 2002) reference, Applicants argue that the results are dosage specific and that the data highlighted by the Examiner in figure 2 corresponds to a single dose with no indication of that being the optimal dose. Applicants argue that the McCluskie et al. (Vaccine 19: 2657-2660, 2001) and Jones et al. (Vaccine 17: 3065-3071, 1999) references similarly demonstrate that higher doses may be necessary for an immune response and not that phosphorothioate nucleotide analogs are not immunostimulatory. In response, the Examiner cited the art listed above to demonstrate that administering any phosphorothioate oligonucleotide is unpredictable. These teachings combined with the fact that Applicants have not provided sufficient evidence in the disclosure would lead one of ordinary skill in the art to conclude that administering any phosphorothioate oligonucleotide analog to stimulate an immune response is unpredictable. Again, the Examiner points out that the data provided in the specification is limited to only one species of phosphorothioate oligonucleotide, ISIS 2105, and is not sufficient to provide enablement for the entire genus of phosphorothioate analogs given the teachings of Vollmer et al., Ratajczak et al., as well as Mojcik et al., Branda et al., and McIntyre et al.

Lastly, Applicants argue that the specification must be enabled as of the filing date. Applicants argue that since the effective filing date of the instant application is March 25, 1994 requires consideration of what was known at the time of filing and that "publications dated after the filing date providing information publically disclosed after the filing date cannot be used to show what was known at the time of filing, see Remarks, page 10, 2nd full paragraph, lines 1-10. The Examiner does not concur. While it is true that publications dated after the filing date providing information publicly

first disclosed after the filing date generally cannot be used to show what was known at the time of filing, post filing art can be used to support an Examiner's position of unpredictability so that a person skilled in the art would not have believed that the success with one specific species, in this case one specific phosphorothioate oligonucleotide sequence, could be extrapolated successfully to all phosphorothioate oligonucleotide sequences, see MPEP § 2164.05(a) [R-2], last paragraph and *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-1514 (Fed. Cir. 1993).

Therefore, one of ordinary skill in the art would conclude that methods of eliciting an immune response by the administration of any phosphorothioate oligonucleotide analog would require undue experimentation in order to use the invention as claimed by the Applicants.

Double patenting

6. The rejection of claims 26, 28, 29, and 30, on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,727,230 (Hutcherson et al.) in view of U.S. Patent 5,356,882 (Walker et al., effective filing date July 13, 1990) is maintained.

Since Applicants have not argued this rejection, it is maintained for the reasons of record provided in the previous Office action.

Conclusion

7. No claim is allowed.

8. No new grounds of rejection were presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Humphrey, Ph.D.

October 12, 2006

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER